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EXAMINER
GOON, SCARLETT Y

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
12/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/579,620	DEFREES ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *4-6,8-10,14,15,17,18,20-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,11-13,16 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 November 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 12 November 2010 in which claims 3 and 19 were cancelled, and claims 1, 2, 4-6, 14, 17 and 20-22 are amended to change the scope and breadth of the claims.

Claims 1, 2, 4-18 and 20-28 are pending in the instant application.

Claims 4-6, 8-10, 14, 15, 17, 18, 20-26 and 28 were previously withdrawn from further consideration in the Office Action dated 6 July 2010 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim. Applicants are requested to note that although claims 8-10 were indicated as being withdrawn in the previous Office Action, the previous Office Action also inadvertently rejected these claims over the prior art. This Office Action corrects the oversight and show that claims 8-10 are properly withdrawn and not currently rejected over the prior art.

Claims 1, 2, 7, 11-13, 16 and 27 will be examined on its merits herein.

Rejections Withdrawn

Applicants' amendment, filed 12 November 2010, with respect to the rejection of claims 1, 2, 7, 11-13, 16 and 27 under 35 USC § 102(b), as being anticipated by WO 03/031464 to DeFrees *et al.*, as evidenced by journal article publication by Oh-eda *et al.*, have been fully considered and are persuasive because DeFrees *et al.* do not teach a peptide conjugate comprising a R^1 moiety as recited in the amended claim limitations. This rejection has been **withdrawn**.

Applicants' amendment, filed 12 November 2010, with respect to the rejection of claims 1, 2, 7, 11-13, 16 and 27 under 35 USC § 103(a), as unpatentable over EP 0605963 A2 to Wright, as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.*, in view of PG Pub No. US 2002/0016003 to Saxon *et al.*, in view of U.S. Patent No. 5,643,575 to Martinez *et al.*, in view of journal article publication by Monaco *et al.*, as evidenced by Nagata *et al.*, as evidenced by journal article publication by Oh-eda *et al.*, have been fully considered and are persuasive because the combined teachings of the prior art do not teach a peptide conjugate comprising a R^1 moiety as recited in the amended claim limitations. This rejection has been **withdrawn**.

The provisional rejection of claims 1, 2, 16 and 27 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending U.S. application no. 12/418,530, is withdrawn as the copending application has been abandoned. This rejection has been **withdrawn**.

Applicants' amendment, filed 12 November 2010, with respect to the rejections of various claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over various claims U.S. Patent No. 7,138,371, U.S. Patent No. 7,173,003, U.S. Patent No. 7,416,858, U.S. Patent No. 7,473,680, U.S. Patent No. 7,691,603, U.S. application no. 10/585,385, U.S. application no. 11/794,560, U.S. application no. 11/867,553, U.S. application no. 11/597,258, U.S. application no. 11/866,969, U.S. application no. 12/152,587, U.S. application no. 12/443,428, U.S. application no. 12/496,595, and U.S. application no. 12/663,056, have been fully

considered and are persuasive because the U.S. Patents and copending applications do not teach a peptide conjugate comprising a R^1 moiety as recited in the amended claim limitations. These rejections have been **withdrawn**.

In view of the cancellation of claims 3 and 19, all rejections made with respect to claims 3 and 19 in the previous Office Action are withdrawn. These rejections have been **withdrawn**.

Priority

This application is a National Stage entry of PCT/US04/41004 filed on 3 December 2004 and claims priority to U.S. provisional application no. 60/526,769 filed on 3 December 2003, U.S. provisional application no. 60/539,387 filed on 26 January 2004, U.S. provisional application no. 60/555,813 filed on 23 March 2004, U.S. provisional application no. 60/570,282 filed on 11 May 2004, U.S. provisional application no. 60/592,744 filed on 29 July 2004, U.S. provisional application no. 60/614,518 filed on 29 September 2004, U.S. provisional application no. 60/623,387 filed on 29 October 2004.

Applicants' claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional

application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir 1994). Also see MPEP § 201.11.

The disclosure of the prior-filed applications, U.S. provisional application no. 60/623,387 filed on 29 October 2004, U.S. provisional application no. 60/614,518 filed on 29 September 2004, U.S. provisional application no. 60/592,744 filed on 29 July 2004, U.S. provisional application no. 60/570,282 filed on 11 May 2004, U.S. provisional application no. 60/555,813 filed on 23 March 2004, U.S. provisional application no. 60/539,387 filed on 26 January 2004, and U.S. provisional application no. 60/526,769 filed on 3 December 2003, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior filed applications do not disclose a granulocyte colony stimulating factor peptide comprising the moiety as recited in claim 1. More particularly, the prior filed applications do not disclose a moiety of claim 1 which encompasses all of the limitations of G and R^1.

Thus, the priority date of the instant claims **1, 2, 7, 11-13, 16 and 27** is deemed to be the filing date of the only application that provides support for the instantly filed application, PCT/US04/41004, filed on 3 December 2004. If Applicant disagrees, Applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority

for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to said priority date.

Response to Arguments

Applicants argue that the structures of the pending claims are entitled to the priority date of at least 29 September 2004, which is the filing date of U.S. provisional application 60/614,518. Specifically, Applicants cite paragraph 0109 et seq. for support of the PEG structures of the pending claims. Additionally, Applicants argue that support for the PEG structures is further provided in text form at paragraph 0117 of U.S. provisional application no. 60/592,744, filed on 29 July 2004. Applicants further argue that exemplary support for the PEG-modified sialic acid moiety can be found in U.S. provisional application no. 60/526,796, filed on 3 December 2003, at p. 24, lines 1-7.

The cited sections of the provisional application have been carefully reviewed but are still not considered to provide support for the full scope of claim 1. Specifically, there is no disclosure in the cited sections of the provisional application, or anywhere else within the provisional application, for the limitation wherein G is –C(O)(C_1-C_6)alkyl. Additionally, there is no disclosure that L can be any substituted or unsubstituted alkyl, or any substituted or unsubstituted heteroalkyl. While it is noted that the provisional application provides examples of suitable linkers, exemplary linkers are not sufficient to

define the entire genus claimed. Applicants are requested to note that while the provisional applications provide support for specific embodiments of claim 1, they do not provide support for the full scope of the claims. In order to receive the benefit of the priority date of these earlier applications, the prior-filed applications must provide support for the full scope of the claims.

Thus, it is maintained that the priority date of the instant claims **1, 2, 7, 11-13, 16 and 27** is deemed to be the filing date of the only application that provides support for the instantly filed application, PCT/US04/41004, filed on 3 December 2004.

Information Disclosure Statement

The information disclosure statement (IDS) dated 12 November 2010 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 12 November 2010, wherein the limitations in pending claim 1 as amended now have been changed; claims 2, 7, 11-13, 16 and 27 depend from claim 1. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 6 July 2010, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1, 2, 7, 11-13, 16 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 03/031464 to DeFrees *et al.* (IDS dated 3 June 2010), as evidenced by journal article publication by Oh-eda *et al.* (of record), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; IDS dated 3 June 2010), in view of journal article publication by Felix *et al.* (IDS dated 3 June 2010), in view of WO 99/55376 A1 to El-Tayar *et al.* (of record).

DeFrees *et al.* disclose methods and compositions for remodeling a peptide molecule, including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide. Modifying groups include water-soluble polymers, such as poly(ethylene glycol) (p. 152, lines 7-25). The use of poly(ethylene glycol) to derivatize peptide therapeutics has been demonstrated to reduce the immunogenicity of the peptides and prolong their clearance time from circulation (p. 4, lines 3-9). The PEG moiety has been shown to be attached via a peptide amino acid residue (p. 4, lines 13-20) or an oxidized glycosyl residue of the peptide (p. 4, line 28 – p. 5). In one embodiment, a conjugate is formed between G-CSF and a modifying group, wherein the modifying group is covalently attached to the G-CSF peptide through an intact glycosyl linking group, and the G-CSF peptide comprises a glycosyl residue having a formula as indicated (p. 23, lines 8-23; p. 297, line 19 – p.298, line 2). The modifying group exemplified in the disclosure of DeFrees *et al.* is poly(ethylene glycol) molecules, such as those in formula 3 (p. 154, line 28 – p. 156). The PEG molecules disclosed on p. 156 meet the limitations of the R^1 structure of the instant claims. DeFrees *et al.* further disclose a pharmaceutical composition

comprising a pharmaceutically acceptable diluent and a covalent conjugate between a polymer and a glycosylated or non-glycosylated peptide, wherein the polymer is conjugated to the peptide via an intact glycosyl linking group interposed between and covalently linked to both the peptide and the polymer (p. 21, lines 9-12). Scheme 3 discloses a modified glycoPEG-ylated compound, such as albumin-PEG-SA-EPO, wherein EPO represents erythropoietin and SA represents sialic acid, which can be used in a method for extending the blood-circulation half-life of selected peptides (p. 149, Scheme 3 and lines 1-10). Formula 1 discloses the structure of a remodeled N-linked glycan, comprising a tri-mannosyl core, preferably linked to an asparagine residue on a peptide backbone (p. 129, lines 10-21). Figure 9 depicts well-known strategies for the synthesis of biantennary, triantennary and even tetraantennary glycan structures beginning with the trimannosyl core structure. Methods for the modification of O-linked glycans wherein the peptide is modified with a GalNAc donor, followed by Gal and SA via the use of appropriate glycosyltransferases is also disclosed (p. 140, lines 20-28). The remodeled peptide has the structure as shown in Formula (2), wherein X^2 is a sialic acid residue and f = 0 or 1 (p. 137, line 2 – p. 138, line 14). The modifying group can be attached to sialic acid at either the 9-position on the pyruvyl side chain or at the 5-position on the amine moiety of sialic acid (p. 150, lines 5-11). The preparation of CMP-SA-PEG, wherein PEG is attached to the C5 position, is disclosed in Scheme 4 (p. 177) and further exemplified in Example 8 (p. 348, line 4 – p. 351, line 21). Table 2 also discloses CMP-SA compounds wherein the glycerol side chain is modified with PEG, such as on the 9-position (p. 178). Preparation of the 9-

modified CMP-SA compound is disclosed in Scheme 8 (p. 181). Figure 27 provides a schematic representation for the modification of glycan structures on G-CSF with PEG (p. 83, lines 9-14). Additionally, Figure 27A shows that G-CSF has one site for O-linked glycosylation, occurring at position 133 of the peptide backbone. Figure 52 discloses exemplary nucleotide and corresponding amino acid sequences of G-CSF as SEQ ID Nos. 1 and 2, respectively (p. 92, lines 1-3). SEQ ID No. 1 of DeFrees *et al.* has the same sequence as SEQ ID No. 1 of the instant application. Figure 126 discloses the results of an *in vitro* bioassay comparing PEGylated EPO with non-PEGylated EPO (p. 99, lines 22-25). EPO glycoPEGylated with 1 kDa PEG had almost the same activity as the unglycoPEGylated EPO when both were at a concentration of approximately 5 μg/mL. The EPO glycoPEGylated with 10 kDa PEG had approximately half the activity of the unglycoPEGylated EPO when both were at a concentration of approximately 5 μg/mL (p. 363, line 30 - p. 364, line 4).

It is noted that DeFrees *et al.* is silent regarding the glycosylated amino acid and the structure of glycans present on G-CSF. However, as evidenced by Oh-eda *et al.*, *O*-glycoslyation occurs at Thr-133 in hG-CSF, and has the structure NeuAcα2-3Galβ1-3(±NeuAcα2-6)GalNAcol (column 2, first incomplete paragraph).

The teachings of DeFrees *et al.* differ from that of the instantly claimed invention in that DeFrees *et al.* do not disclose the specific branched PEG structures as recited in the instant claims.

The Martinez '575 patent teaches branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and

peptides as a means to extend their circulating half-life *in vivo*. One of the chief advantages for the use of branching polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with (column 2, lines 42-51). Another advantage is that the branched polymers provide the benefits associated with attaching several strands of polymers to a bioeffecting material, but require substantially fewer conjugation sites, which is apparent in therapeutic agents having few available attachment sites (column 2, lines 52-59). The branched polymers are represented by formula (I), $(R)_nL$-A, wherein R is the water-soluble polymer, n is 2 or 3, L is the aliphatic linking moiety covalently lined to R, and A represents the activating functional group (column 3, lines 11-22). The polymers are preferably prepared from methoxypoly (ethylene glycols), or other suitable alkyl substituted poly(alkylene oxide) derivative, such as those containing mono or bis terminal C_1-C_4 groups (column 2, lines 65 - column 3, line 4). Straight-chained non-antigenic polymers such as monomethyl PEG (mPEG) homopolymers are preferred (column 3, lines 4-6). It is preferred that each mPEG chain has a molecular weight of between 200 and about 12,000 Da, with molecular weights of about 5,000 Da being most preferred (column 3, lines 23-29). The variable L preferably includes a multiply-functionalized alkyl group containing up to 13, and more preferably, between 1-10 carbon atoms (column 3, lines 59-63). A heteroatom, such as nitrogen, oxygen or sulfur may be included within the alkyl chain, which may also be branched at a carbon or nitrogen atom. Examples of other linkages between (R) and (L) include ether, amine, urea, and thio and thiol analogs thereof (column 4, lines 14-20). The linkages are

formed by methods well understood by those of ordinary skill in the art. Other suitable linkages and their formation can be determined by reference to U.S. Patent No. 4,179,337. The variable "A" is selected from any functional group that is capable of reacting with 1) an amino group, 2) a carboxylic acid group or reactive carbonyl group, or 3) mercapto or sulfhydryl groups. The variable "A" can also include a spacer moiety located proximal to the aliphatic linking moiety "L" (column 4, lines 47-50). Biologically active molecules of interest include, but are not limited to, proteins, peptides, polypeptides, enzymes, organic molecules of natural and synthetic origin such as medicinal chemicals, and the like (column 7, lines 40-45). Among the list of proteins cited as being of interest are cytokines, such as interleukins, alpha-, beta-, and gamma-interferons and granulocyte colony stimulating factor (column 7, lines 57-64). Example 8 discloses the preparation of a branched PEG structure wherein lysine is the linker conjugated to two linear mPEG compounds (column 13, lines 20-40).

Felix *et al.* teach the synthesis of symmetrically and asymmetrically branched pegylating reagents. PEG-protein conjugates have been shown to have improved bioavailability and therapeutic efficacy stemming from increased resistance to proteolytic degradation, enhanced pharmacokinetic and improved pharmacodynamic properties, and reduced renal clearance (p. 86, column 1, first paragraph). Additionally, many pegylated proteins have been reported to have increased plasma half-lives and reduced antigenicity and immunogenicity (p. 86, column 1, first paragraph). Branched PEGs offer an additional dimension of steric protection to the proteins to which they are linked (p. 86, column 2, bridging paragraph). Lysine has been used successfully as a

spacer for branched PEG structures (p. 86, column 1, last paragraph). It is expected that introduction of additional branches to PEG would provide additional levels of enzymatic protection to the proteins to which they are linked (p. 86, column 2, first full paragraph). Felix *et al.* disclose a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker (p. 87, column 1, Figure 1). Methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent are disclosed in Figure 2 (p. 87).

El-Tayar *et al.* teach PEG-LHRH analog conjugates, where a PEG moiety is covalently bound to a serine residue of a LHRH analog either directly or via a bifunctional linker molecule, such as an amino acid (p. 4, last paragraph). El-Tayar *et al.* teach that branched PEGs are in common use (p. 1, last paragraph). El-Tayar *et al.* disclose serine as one such amino acid bifunctional linker (p. 8).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of DeFrees *et al.*, concerning methods for the preparation of glycosylated G-CSF, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. G-CSF, as a means to extend their circulating half-life *in vivo*, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker, with the teachings of El-Tayar *et al.*, regarding the use of amino acids as bifunctional linkers.

Since both the Martinez ‘575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to use the branched PEG polymers disclosed in the Martinez '575 patent, or by Felix *et al.*, in order to receive the expected benefit that the resulting branched PEGylated G-CSF would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, and El-Tayar *et al.* teach that amino acids can be used as bifunctional linkers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, specifically, any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine. Additionally, since El-Tayar *et al.* teach that amino acids can be used as a linker for conjugation of PEG to a peptide, Felix *et al.* exemplify the use of lysine and glutamate for generating PEG linkers, and serine and cysteine, commonly known amino acids, fall within the definition of a linker useful for conjugation of PEG to a

peptide as defined in the Martinez '575 patent, one of ordinary skill in the art would have a reasonable expectation of success.

It is further noted that DeFrees *et al.* do not expressly teach that PEGylated EPO is tissue protective or essentially non-erythropoietically active, as recited in the instant claims. However, the recitations "is essentially non-erythropoietically active" and "is tissue protective" are considered to be a result of the structural claim limitations. Thus, Applicants' recitations are not considered to further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See also MPEP § 2112.01.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments filed 12 November 2010 with respect to the rejection of claim 3 made under 35 USC § 103(a) as being unpatentable over WO 03/031464 to DeFrees *et al.*, as evidenced by journal article publication by Oh-eda *et al.*, as applied to

claims 1, 2, 7-13, 16 and 27, further in view of U.S. Patent No. 5,643,575 to Martinez *et al.*, in view of journal article publication by Felix *et al.*, in view of WO 99/55376 A1 to El-Tayar *et al.*, have been fully considered but are moot as claim 3 has been canceled. As the limitations of claim 3 have been imported into claim 1, Applicants' arguments will be addressed insofar as they are applicable to the pending claims.

Applicants argue that neither the Martinez '575 patent nor Felix *et al.* teach a method by which the presently claimed structures could be prepared. Specifically, Applicants argue that the Martinez '575 patent only exemplify conditions wherein PEG groups are attached via an amide linkage, and provides no teaching or suggestion of how to prepare branched PEG structures using an ether or thioether as recited in the pending claims. Similarly, Applicants argue that Felix *et al.* do not teach reagents and/or reaction conditions for employing amino acids other than lysine. Applicants' arguments have been carefully considered but are not deemed persuasive. Applicants are requested to note that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

With regards to the instant rejection, El-Tayar *et al.* expressly teaches that amino acids can be used as linkers for conjugation of PEG to a polypeptide. Furthermore, the Martinez '575 patent and Felix *et al.* have already successfully shown the use of lysine and glutamate as linkers for conjugation of PEG to a polypeptide backbone. Thus, in view of the teachings of the prior art, it is *prima facie* obvious for one of ordinary skill in

the art to substitute serine, or any other amino acid, in place of lysine or glutamate, which were already exemplified in the art. Since El-Tayar *et al.* suggest the use of amino acids as linkers, and lysine and glutamate have been exemplified in the prior art by Felix *et al.* and in the Martinez '575 patent, one of ordinary skill in the art would have a reasonable expectation of success in using serine as the linker. Although Applicants argue that none of the prior art teaches reaction conditions and methods for use of a serine linker, the Martinez '575 patent expressly teaches that "[t]he linkages are formed by methods well understood by those of ordinary skill in the art," and furthermore, expressly teaches that linkers "include ether, amine, urea, and thio and thiol analogs thereof." Thus, it is the Office's position that formation of an amide linkage, such as that exemplified in the art, or the formation of an ether or thiol linkage, such as that suggested in the prior art, is basic organic chemistry knowledge to one of ordinary skill in the art. In view of the teachings of the prior art, if one of ordinary skill in the art desired an ether linkage, one of ordinary skill in the art would know how to modify serine or PEG accordingly such that reaction of the two would yield an ether linkage. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

The rejection is still deemed proper and therefore adhered to.

Section [0002]

Claims 1, 2, 7, 11-13, 16 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 4 December 2008), as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; IDS dated 3 June 2010), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.* (hereinafter referred to as the '778 patent; IDS dated 3 June 2010), in view of PG Pub No. US 2002/0016003 to Saxon *et al.* (IDS dated 3 June 2010), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; IDS dated 3 June 2010), in view of journal article publication by Monaco *et al.* (of record), as evidenced by Nagata *et al.* (of record), as evidenced by journal article publication by Oh-eda *et al.* (of record), in view of journal article publication by Felix *et al.* (IDS dated 3 June 2010), in view of WO 99/55376 A1 to El-Tayar *et al.* (of record).

Wright teaches methods and compounds for modifying polypeptides with PEG or other water-soluble organic polymers. Protein and other similar organic molecules are chemically modified by covalent conjugation to water-soluble organic polymers, such as PEG, because of the desirable properties conferred on the polypeptides by attachment of the water-soluble polymers. The desirable properties include solubility in aqueous solutions, increased stability during storage, reduced immunogenicity, increased resistance to enzymatic degradation, compatibility with a wider variety of drug administration systems, and increased *in vivo* half-life (p. 2, lines 11-16). Conjugation of mPEG to a cysteine residue of EPO is known (p. 3, lines 5-9). However, Wright teaches that it may be advantageous to couple water-soluble reagents to the

carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins (p. 3, lines 38-46). By providing for water-soluble polymer reagents that may be coupled to the carbohydrate moiety of glycoproteins it may be possible to covalently conjugate water-soluble polymers to proteins without substantially adversely affecting the biological activity of proteins that would be adversely affected through coupling at other amino acid residues (p. 3, lines 47-50). Wright teaches that hydrazine and oxylamine derivatives of water-soluble polymers, such as PEG, may be covalently attached to proteins through reactions with aldehyde groups or other suitable functional groups present on the protein of interest (p. 7, lines 5-11). Aldehyde groups may be introduced by partially oxidizing the hydroxyl groups on the polypeptide, such as hydroxyl groups present on the carbohydrate moieties of the polypeptide, with galactose oxidase or periodate (p. 7, lines 11-16). Hydrazide and oxylamine derivatives are further disclosed (p. 7, lines 19-58). Examples of PEG water soluble polymers include polyethylene glycol, methoxypolyethylene glycol, polyethylene glycol homopolymers, polypropylene glycol homopolymers, copolymers of ethylene glycol with propylene glycol (p. 7, line 58 – p. 8, line 3). Wright further teaches that the disclosed preparation may be administered alone or in an admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice (p. 12, lines 14-21). Polypeptides of interest for water-soluble polymer derivatization

include hormones, lymphokines, cytokines, growth factors, enzymes, vaccine antigens, and antibodies (p. 4, lines 26-29). Methods for the synthesis of mPEG-hydrazide from mPEG-OH (p. 12, line 55 - p. 13, line 37) and mPEG-semicarbazide from mPEG-NH_2 (p. 13, line 50 – p. 14, line 16) are further disclosed. Methods for the modification of a peptide with mPEG-hydrazide and mPEG-semicarbazide are further exemplified with EPO, wherein EPO is oxidized with sodium periodate followed by conjugation of the resulting aldehyde to PEG (p. 18, line 26 - p. 19, line 14). It is noted that Wright does not expressly teach which carbohydrate group is oxidized to an aldehyde in the presence of sodium periodate. However, as evidenced by Kinstler *et al.*, 10 mM sodium periodate oxidation of EPO targets the pendant diol of the penultimate glycosyl unit sialic aicd residue (p. 11, lines 1-10 and p. 19, lines 29-33).

Although Wright expressly disclose cytokines as polypeptides that would be useful when conjugated to water-soluble polymers, such as PEG, Wright does not expressly disclose specific cytokines, such as granulocyte colony stimulating factor, as recited in the instant claims. Additionally, Wright does not disclose the specific linker and the branched PEG structures as recited in the instant claims.

The Ishikawa ‘778 patent discloses a polyethylene glycol-modified human granulocyte colony stimulating factor (G-CSF). The polyethylene glycol (PEG) is covalently bound through amino acid residues of the polypeptide of human G-CSF, such as those having a free amino group (e.g. lysine and the N-terminal amino acid residue) and those having the free carboxyl group (e.g. aspartic acid, glutamic acid and the C-terminal amino acid residue) (column 2, line 66 – column 3, line 8). The PEG

modified human G-CSF has a more enduring pharmacological effect, which may be possibly attributed to its prolonged half-life in the body (column 4, lines 16-18). The PEG modified human G-CSF has essentially the same biological activity as an intact human G-CSF and is therefore useful in the treatment of general haematopoietic disorders, including those arising from chemotherapy or from radiation therapy (column 4, lines 22-31). The PEG modified human G-CSF may be formulated into pharmaceuticals containing also a pharmaceutically acceptable diluent, an agent for preparing an isotonic solution, a pH-conditioner, and the like, in order to administer them into a patient (column 4, lines 32-36).

Saxon *et al.* teach a method for covalent modification of molecules. The chemoselective ligation reaction can be carried out under physiological conditions, and involves condensation of a specifically engineered phosphine, which can provide for formation of an amide bond between the two reactive partners resulting in a final product comprising a phosphine oxide, or which can be engineered to comprise a cleavable linker so that a substituent of the phosphine is transferred to the azide of the other molecule (paragraph 0018). The selectivity of the reaction and its compatibility with aqueous environments provides for its application *in vivo* and *in vitro*, e.g. synthesis of peptides and other polymers. Saxon *et al.* disclose the use of a synthetic substrate comprising an abiotic reactive partner, such as the azido compounds of paragraphs 0067-0070, for incorporation into a biopolymer, which is utilized in the glycoprotein biosynthetic pathway. For example, host cells provided with synthetic sialic acid azido-derivatives, such as those disclosed in paragraphs 0067-0070, incorporate these

compounds into the sialic acid biosynthetic pathway, eventually resulting in the incorporation and expression of the synthetic sugar residues on glycoproteins (paragraph 0066). The azido-modified glycoprotein can then undergo a chemoselective ligation reaction with another molecule engineered with a phosphine. The engineered phosphine can be modified to comprise a molecule desired for delivery and conjugation to the azido-target substrate, such as that comprising detectable labels, small molecule drugs, cytotoxic molecules, ligands for binding by a target receptor, tags to aid in purification, and molecules to facilitate selective attachment of the polypeptide to a surface (paragraph 0075). The chemoselective ligation can be performed with a modified phosphine that comprises a cleavable linker. Thus, reaction of i) a first reactant comprising a first molecule of interest engineered with a phosphine comprising a cleavable linker, with ii) a second reactant comprising a second molecule of interest engineered with an azide, results in conjugation of the first molecule of interest to the second molecule of interest via an amide or a thioamide bond, accompanied by the release of nitrogen and an oxidized phosphine byproduct (paragraph 0109). This reaction is further schematically illustrated in paragraph 0109. As shown in Example 6, cells incorporate N-azidoacetylmannosamine into cell surface glycans, as detected by labeling of the cells with biotin modified with a phosphine group, followed by FITC-avidin staining (paragraph 0198). Example 7 illustrates a method wherein two peptides, one modified with an azido group, and the other modified with a phosphine group with a cleavable linker, are conjugated together to form an amide bond between the two peptides. Saxon *et al.* further disclose that previous work showed that incorporation of

a ketone-bearing group, such as a levulinoyl group, can be expressed on glycoproteins as SiaLev, wherein the levulinoyl group is present at the 5-position of sialic acid, and that the ketone group on SiaLev can be chemoselectively conjugated to compounds or other molecules bearing a hydrazide group (paragraphs 0008-0010).

The teachings of the Martinez '575 patent were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

Monaco *et al.* teach a method for expression of recombinant human granulocyte colony-stimulating factor in CHO dhfr$^-$ cells. The system yields a larger proportion of clones producing high amounts of recombinant protein, as compared to clones from the classical co-transfection protocol (p. 149, subheading "Conclusions"). The G-CSF sequence is that same as the sequence published by Nagata *et al.* As evidenced by Nagata *et al.*, the human G-CSF sequence of Monaco *et al.* is the same as SEQ ID No. 1 of the instant application. Furthermore, it is noted that Monaco *et al.* is silent regarding the site of glycosylation, and the structure of glycosyl residues, on the HG-CSF polypeptide backbone in CHO cells. As evidenced by Oh-eda *et al.*, *O*-glycoslyation occurs at Thr-133 in hG-CSF, and has the structure NeuAcα2-3Galβ1-3(±NeuAcα2-6)GalNAcol (column 2, first incomplete paragraph).

The teachings of the Felix *et al.* and El-Tayar were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright, concerning the modification of peptides, such as cytokines, with water-soluble polymers, such as PEG, with the

teachings of the Ishikawa ‘778 patent, concerning conjugation of PEG to human G-CSF via the amino acids of the polypeptide to increase its half-life in the body, with the teachings of Saxon *et al.*, regarding chemoselective ligations involving a ketone group with a hydrazide group, or an azido group with a phosphine, with the teachings of the Martinez ‘575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. G-CSF, as a means to extend their circulating half-life *in vivo*, with the teachings of Monaco *et al.*, regarding the cloning and expression of recombinant human granulocyte colony-stimulating factor in CHO cells, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker, with the teachings of El-Tayar *et al.*, regarding the use of amino acids as bifunctional linkers.

Since Wright teaches that polypeptides, such as cytokines, are advantageously conjugated to PEG polymers through the glycosylations present on those peptide molecules rather than to the amino acids of the polypeptide backbone because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins, and the Ishikawa ‘778 patent teaches that conjugation of PEG to human G-CSF via the amino acids of the polypeptide increases its half-life in the body, one of ordinary skill in the art would have been motivated to substitute the conjugation method of the Ishikawa '778 patent with that disclosed by Wright, with the reasonable expectation that it would also yield a PEG

conjugated human G-CSF polypeptide with increased half-life in the body. Furthermore, as Wright teaches that conjugation of polypeptides to PEG via the glycosyl residues present on the polypeptide are advantageous as compared to conjugations made directly on the polypeptide amino acids, and the Martinez '575 patent teaches that branched, non-antigenic polymers can be conjugated to biologically active molecules, such as cytokines, as a means to extend their circulating half-life *in vivo*, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate branched PEG polymers to human G-CSF via the glycosylations present on the macromolecules, as described by Wright. Since both Wright and the Martinez '575 patent teach conjugation of PEG to biological macromolecules as a means to extend their serum half-life, and Wright further teaches that cytokines can be conjugated using their disclosed method, one of ordinary skill in the art would reasonably expect that the use of branched PEG plymers, as disclosed in the Martinez '575 patent, for conjugation to a peptide using the method disclosed by Wright, would result in PEGylation of G-CSF at the glycosyl moiety present on G-CSF.

Furthermore, as Wright teaches that PEG-hydrazide polymers are conjugated to the carbohydrate moiety of biological macromolecules by oxidizing the carbohydrate moiety to an aldehyde or other suitable functional group, one of ordinary skill in the art would have been motivated to use this same PEG-hydrazide chemistry for conjugation of PEG onto the carbohydrate residue of glycoproteins expressing a ketone group, such as that present on SiaLev, as disclosed by Saxon *et al.* Since Saxon *et al.* teach that biotin-hydrazide can be selectively conjugated to the ketone group of SiaLev, which is

expressed on the terminus carbohydrate residue of a glycoprotein, one of ordinary skill in the art would reasonably expect that substitution of biotin-hydrazide with PEG-hydrazide would yield a predictable result. One of ordinary skill in the art would consider the conjugation methods disclosed by Saxon *et al.* to be an advantageous method over that described by Wright because it eliminates the need for an oxidation step on the carbohydrate residue.

With regards to obtaining G-CSF containing a terminal SiaLev group on its glycans, Monaco *et al.* teach the expression of rhG-CSF in a CHO system. Thus, based on the combined teachings of Saxon *et al.* and Monaco *et al.*, one of ordinary skill in the art would reasonably expect that expression of G-CSF in the CHO system in the presence of a mannosamine compound as disclosed by Saxon *et al.*, would predictably yield G-CSF modified with SiaLev on the terminus of its glycans. Moreover, as Saxon *et al.* teach that azido groups can be introduced onto sialic acids present on glycoproteins using a similar method to that of SiaLev, and that the azido groups chemoselectively react with phosphine groups, one of ordinary skill in the art would have been motivated to alternately modify the PEG-hydrazide compounds, disclosed by Wright, into PEG-phosphine compounds for conjugation to azido groups introduced onto the sialic acid residue of glycoproteins. One of ordinary skill in the art would have been motivated to select the azide-phosphine chemistry, in order to receive the expected benefit, as disclosed by Saxon *et al.*, that these two groups are abiotic to cell surfaces. One of ordinary skill in the art would have been motivated to conjugate PEG onto G-CSF, in order to receive the expected benefit, as disclosed by Wright, that conjugation

of PEG to a peptide increases its solubility in aqueous solutions, stability during storage, and resistance to enzymatic degradation, and reduces its immunogenicity, as well as increasing its *in vivo* half-life. Moreover, as disclosed by Wright, it may be advantageous to couple PEG to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins. Thus, although Saxon *et al.* exemplify conjugation of a hydrazide or phosphine group onto sialic acid derivatives expressed on glycoproteins as a detection method, Saxon *et al.* do disclose that small molecules, peptide, ligands, etc., could be conjugated to the azido or ketone group introduced onto sialic acid. As such, in view of the teachings of Wright, it would have been *prima facie* obvious to one of ordinary skill in the art that other molecules, such as PEG-hydrazide or PEG-phosphine, could be conjugated to the sialic acid derivatives present on the glycoproteins.

Since both the Martinez ‘575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to modify the branched PEG polymers disclosed in the Martinez '575 patent, or by Felix *et al.*, with hydrazide reactive groups for conjugation to glycans present on the peptide, such as that disclosed by Wright, in order to receive the expected benefit that the resulting branched

PEGylated G-CSF would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

With regards to the specific branched PEG structures as recited in the instant claims, since Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, and El-Tayar *et al.* teach that the amino acids can be used as bifunctional linkers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, specifically, any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine. Additionally, since El-Tayar *et al.* teach that amino acids can be used as linker for conjugation of PEG to a peptide, Felix *et al.* exemplify the use of lysine and glutamate for generating PEG linkers, and serine and cysteine, commonly known amino acids, fall within the definition of a linker useful for conjugation of PEG to a peptide as defined in the Martinez ‘575 patent, one of ordinary skill in the art would have a reasonable expectation of success.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments filed 12 November 2010 with respect to the rejection of claim 3 made under 35 USC § 103(a) as being unpatentable EP 0605963 A2 to Wright, as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.*, in view of PG Pub No. US 2002/0016003 to Saxon *et al.*, in view of U.S. Patent No. 5,643,575 to Martinez *et al.*, in view of journal article publication by Monaco *et al.*, as evidenced by Nagata *et al.*, as evidenced by journal article publication by Oh-eda *et al.*, in view of journal article publication by Felix *et al.*, in view of WO 99/55376 A1 to El-Tayar *et al.*, have been fully considered but they are moot as claim 3 has been canceled. As the limitations of claim 3 have been imported into claim 1, Applicants' arguments will be addressed insofar as they are applicable to the pending claims.

Applicants argue that the pending claims are directed to a G-CSF peptide covalently linked to a branched PEG residue having particularly, serine or cysteine–based structures via an intact glycosyl group, but that the teachings of Wright *et al.*, the Kinstler '398 patent, Ishikawa *et al.*, the Martinez '575 patent, Nagata *et al.*, and Oh-eda *et al.* do not teach or suggest a G-CSF peptide coupled to a modifying group via an "intact glycosyl linking group" as recited in the pending claims. Applicants' arguments have been considered but are not persuasive. Applicants are requested to note that the rejection was made over the combined teachings of the prior art, which also included the teachings of Saxon *et al.* Thus, one cannot show nonobviousness by attacking

references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As discussed in the rejection above, since Saxon *et al.* teach that biotin-hydrazide can be selectively conjugated to the ketone group of SiaLev, which is expressed on the terminus carbohydrate residue of a glycoprotein, one of ordinary skill in the art would reasonably expect that substitution of biotin-hydrazide with PEG-hydrazide would yield a predictable result. One of ordinary skill in the art would consider this to be an advantageous method over the chemistry as taught in Wright *et al.* because it eliminates the need for an oxidation step on the carbohydrate residue.

Applicants further argue that the teachings of Saxon *et al.* that these displayed ketones can then be further modified "with any moiety bearing a hydrazide or aminooxy group" overreaches the actual disclosure of the reference cited because Mahal *et al.* only recite the linkage of biotinamido-caproyl hydrazide, a small biotin-based molecule. This argument has been fully considered but is not persuasive. As Applicants noted, Mahal *et al.* expressly speculate that "[i]n principle, any hydrazide-derivatized molecule can be used to selectively remodel the surface of ketone-expressing cells." Thus, the teachings of Saxon *et al.* are merely re-iterating what is disclosed by Mahal *et al.* Although Mahal *et al.* only exemplify their disclosed method using a small biotin-based molecule, the suggestion of using larger molecules is presented. Therefore, it is the Office's position that the combined teachings of the prior art, including the teachings of Saxon *et al.* that the reaction between a ketone and a hydrazide, and that between an

azide and a phosphine, are advantageous because the reactions are chemoselective, and the teachings of Wright that it would be advantageous to couple PEG-hydrazides to the oxidized moiety of a carbohydrate residue on a glycoprotein rather than to the polypeptide backbone amino acids because of steric hindrance and active sites present in the amino acids, would motivate one of ordinary skill in the art to arrive at the instantly claimed invention. Furthermore, contrary to Applicants' arguments, as Wright exemplifies the conjugation of a PEG-hydrazide to an aldehyde group, the use of PEG-hydrazide for conjugation to the ketone group of SiaLev, as disclosed by Saxon *et al.*, or Mahal *et al.*, does not overreach the actual disclosure of the cited references. Even in the absence of such motivation, based on the combined teachings of the prior art, one of ordinary skill in the art would have tried preparing EPO modified with SiaLev and conjugating the modified glycopeptide with PEG-hydrazide. The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. at 398 (2007), 82 USPQ2d at 1397. See also MPEP § 2143.

It is noted that Applicants further argue that one of ordinary skill in the art would not have reasonably believed, based on the disclosures of Mahal *et al.* and Saxon *et al.*, that PEG would be successfully conjugated using the reactions and reagents provided therein. Specifically, Applicants cite that limitations of azide coupling is shown in Figure

13, and described in Example 7, wherein an acetate-amide linkage is unsuccessfully attempted. As Saxon *et al.* posit that a "rigid linker" may be necessary for the desired reaction to take place, Applicants argue that one of ordinary skill in the art would not have reasonably expected a relatively fluid molecule such as PEG to be suitable for conjugation using the methods disclosed therein. Applicants' arguments have been fully considered, but are not persuasive. Applicants are requested to note that Saxon *et al.* disclose two different chemoselective reactions, that between a ketone and a hydrazide or aminooxy group (as disclosed previously by Mahal *et al.*), and that between an azido group and a phosphine. Therefore, even assuming arguendo that the one of ordinary skill in the art would not have a reasonable expectation of success in conjugating a phosphine-PEG to an azido sialic acid residue that is expressed on EPO, which it is the Examiner's position that there is a reasonable expectation of success, Applicants are requested to note that the chemoselective ligation between a ketone and a hydrazide or aminooxy group is also taught. As stated in MPEP 2123 [R-5], "[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). Therefore, contrary to Applicants' arguments that one of ordinary skill in the art would not have a reasonable expectation of success, because Wright expressly teaches conjugation of PEG-hydrazide to an oxidized aldehyde residue of sialic acid on the EPO peptide, one of ordinary skill in the art would

reasonably expect that conjugation of PEG-hydrazide to a ketone moiety present on sialic acid to behave similarly, albeit the reaction may be slower as aldehydes are known to be more reactive than ketones. Nevertheless, one of ordinary skill in the art would reasonably expect the reaction to proceed and yield the claimed compound.

Applicants also argue that none of the cited references provide branched PEGs as presently claimed. This argument was addressed in the subheading "Response to Arguments" in section [0001] above.

Thus, the rejection is still deemed proper and therefore maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Section [0001]

Claims 1, 2, 7, 11-13, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 215-245 of copending U.S. application no. 11/652,467.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a granulocyte-colony stimulating factor peptide conjugate comprising a modifying group wherein the modifying group is covalently attached to the peptide at an amino acid of the peptide via an intact glycosyl linking group. The peptide is glycosylated at a threonine residue. The glycosyl residue has the formula as indicated in claim 216. The modifying group is a water soluble polymer selected from the group consisting of peptides, saccharides, poly(ethers), poly(amines and poly(carboxylic acids). The water soluble polymer comprises polyethethylene glycol. The claims of the instant application are also drawn to a composition comprising the granulocyte-colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units. The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 7, 11-13, 16 and 27 are seen to be anticipated by claims 215-245 of copending U.S. application no. 11/652,467.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Section [0002]

Claims 1, 2, 7, 16 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending U.S. application no. 11/166,404.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a granulocyte colony stimulating factor conjugate comprising a glycosyl linking group attached to an amino acid residue of said peptide, said glycosyl linking group comprising a modified sialic acid residue having the formula as indicated in claims 1 and 21, and a pharmaceutical composition comprising the said granulocyte colony stimulating factor conjugate. The structures of the glycosyl residue are as shown in claims 4, 10, 11, 14, 24, 25 and 35. The copending application is also drawn to a method of stimulating inflammatory leukocyte production in a mammal, and a method of treating infection in a subject in need thereof, comprising administering the claimed granulocyte colony stimulating factor peptide conjugate.

The claims of the instant application are drawn to a granulocyte colony stimulating factor peptide comprising the moiety as shown in claim 1. The claimed moiety includes structures that encompass sialic acid modified with poly(ethylene glycol) units. The structure of the glycosyl moiety is as disclosed in claims 7-9. The instant application is also drawn to a pharmaceutical formulation comprising the

granulocyte colony stimulating factor peptide according to claim 1, and a pharmaceutically acceptable carrier (claim 27).

Thus, the instant claims 1, 2, 7, 16 and 27 are seen to be anticipated by claims 1-41 of copending U.S. application no. 11/166,404.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants' intent that the obviousness-type double-patenting rejections above be held in abeyance until one or more claims in the present claim are otherwise deemed allowable, in the reply filed on 12 November 2010, is acknowledged.

The rejections are still deemed proper, with modifications made to account for Applicants' amendment, and therefore maintained.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623